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Dopaminergic Reward System in the Development of Food Preferences, Obesity and Addictive Behaviors

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In this thesis, the role of the dopaminergic reward system in the development of food preferences, obesity and addictive behaviors has been studied. This included animal studies analyzing mice exposed to a maternal HFD during pregnancy and lactation and human studies that analyzed the genetic association studies of obese individuals participating in a weight reduction program.

The animal studies examined the influence of a maternal HFD during pregnancy and lactation on the development of food preferences, dopamine reward signaling and body weight gain in the offspring. Here, the role of dopamine in the hedonic control of food intake was studied. C57BL/6 mice dams were fed either a regular chow diet or a HFD containing 60% of energy from fat three weeks prior to mating, during pregnancy and lactation. After weaning, all offspring were maintained on a chow diet. We found that the offspring born to HF-fed dams exhibited an increased preference for HF foods, sucrose and ethanol. We assume that the changes in food preferences are related to altered dopamine-related gene expression as assayed by qPCR. A tendency for decreased TH and DAT expression within the VTA of HFD offspring was observed. Moreover, dopamine D1 and D2 receptor expression in the NAc-shell was increased, whereas dopamine D2 receptor expression in the mPFC was reduced. Studies on body weight gain revealed that HFD offspring were significantly heavier than controls at weaning. However, when maintained on a chow diet, there was no significant body weight difference in adult female offspring. Male offspring born to HF-fed dams even revealed reduced body weights. Moreover, adult female HFD offspring exposed to a chronic HFD did not exhibit increased weight gain. When offspring were offered the choice between a chow and a HFD after weaning, body weights of adult offspring born to HF-fed dams were not significantly different from controls. Male offspring even demonstrated a reduced body fat ratio and an increased lean mass as assessed by CT scans. Since the offspring born to HF-fed dams did not reveal increased adiposity, we assume that besides hedonic mechanisms, homeostatic pathways are involved in the control of the offspring's body weight. As a hint to metabolic impairments, we found increased plasma levels of free fatty acids and triglycerides in adolescent male offspring and increased fasting insulin levels in adult female offspring born to HF-fed dams.

The human studies focused on the genetic mechanisms in the control of body weight. Therefore, the influence of the D2D receptor Taq1A polymorphism on weight reduction and weight maintenance was studied in obese participants during a weight reduction program. Here, the role of dopamine in the control of body weight was studied. OPTIFAST®52 is a medically monitored weight reduction program for severely obese individuals of at least 18 years of age and with a BMI of 30 kg/m^2 or higher. In the weight reduction phase (12 weeks) participants reduced their weight with the help of a formula diet, whereas in the weight maintenance phase (40 weeks) they chose their food individually. The dopamine D2 receptor Taq1A polymorphism was assayed by PCR-RFLP analysis in 135 female and 67 male participants aged between 18 and 72 years. Participants carrying the A1A1 or A1A2 genotype

were considered A1(+), whereas participants with the A2A2 genotype were considered A1(-). We conducted a per protocol analysis and found that there was no difference in BMI between A1(+) and A1(-) participants who completed the program. However, younger A1(+) participants aged between 21 and 40 years showed an increased BMI at the beginning of the program, after the weight reduction phase and after the weight maintenance phase. While there was no significant difference in the weight loss of younger A1(+) and A1(-) participants during the weight reduction phase, A1(+) participants exhibited an increased weight regain during the weight maintenance phase. Moreover, younger A1(+) participants revealed increased plasma insulin levels and decreased HDL levels at the beginning and the end of the program. The A1 allele has previously been associated with a reduced dopamine D2 receptor density in the striatum. Thus, we assume that the impaired weight maintenance in younger A1(+) participants may be due to compulsive eating due to a hypofunctioning reward system. Consequently, it is likely that the elevated body weights of younger A1(+)-carriers derive from difficulties in weight stabilization earlier in the lives of these subjects.

The results of the thesis demonstrate that the dopaminergic reward system is substantially involved in the development of food preferences and addictive behaviors as well as in the control of body weight. Our findings underline a mutual interaction between the dopaminergic reward circuitry and the hedonic control of food intake. On the one hand, palatable nutrition has the potential to alter the programming of the reward circuitry. On the other hand, reward pathways mediate the hedonic control of food intake. Conclusively, our findings confirm that environmental as well as genetic factors influence the interaction between the dopaminergic reward system and the hedonic control of food intake.